Complete Summary

GUIDELINE TITLE

Systemic diseases in pregnancy.

BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Systemic diseases in pregnancy. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007 Apr 13 [Various].

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Finnish Medical Society Duodecim. Systemic diseases in pregnancy. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2006 Aug 30 [Various].

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.
- September 17, 2007, Haloperidol (Haldol): Johnson and Johnson and the U.S. Food and Drug Administration (FDA) informed healthcare professionals that the WARNINGS section of the prescribing information for haloperidol has been revised to include a new Cardiovascular subsection.
- August 16, 2007, Coumadin (Warfarin): Updates to the labeling for Coumadin to include pharmacogenomics information to explain that people's genetic makeup may influence how they respond to the drug.
- May 2, 2007, Antidepressant drugs: Update to the existing black box warning on the prescribing information on all antidepressant medications to include

warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Systemic diseases in pregnancy, including:

- Heart and vascular diseases (hypertension, heart disease)
- Thrombotic complications
- Metabolic disorders (diabetes, hypothyroidism, hyperthyroidism, obesity)
- Neurological diseases (epilepsy, migraine, disturbances of cerebral circulation)
- Renal diseases
- Rheumatic disorders
- Psychiatric problems
- Bronchial asthma
- Cancer

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Cardiology
Endocrinology
Family Practice
Internal Medicine
Nephrology
Neurology
Obstetrics and Gynecology
Oncology
Psychiatry
Rheumatology

INTENDED USERS

Health Care Providers
Physicians

GUIDELINE OBJECTIVE(S)

Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.

TARGET POPULATION

Women with systemic diseases who are pregnant or considering pregnancy

INTERVENTIONS AND PRACTICES CONSIDERED

Management/Treatment

General

1. Preconception examination and counseling by both the disease specialist and an obstetrician
2. Close monitoring of systemic disease throughout gestation
3. Collaboration between prenatal clinic and maternity hospital

Heart and Vascular Diseases

1. Positioning in left lateral recumbent position for examination or treatment

Hypertension

1. Close monitoring and hospitalization, as needed
2. Antihypertensive drugs
3. Avoidance of angiotensin-converting enzyme (ACE)-blocking agents and diuretics

Heart Diseases

1. Treatment based on disease and condition of patient

Thrombotic Complications

1. Laboratory tests for AT_{III}, protein-C, protein-S, and activated partial thromboplastin time (APTT)
2. Prophylactic treatment with low-molecular-weight heparin or subcutaneous unfractionated heparin
3. Warfarin in patients with a cardiac prosthetic valve

Metabolic Disorders

Diabetes

1. Monitoring at 1- to 2-week intervals plus short stay in antenatal ward of obstetric department
2. Insulin therapy (multi-injection treatment)

Hypothyroidism

1. Increased dosage of thyroxine with biochemical monitoring (thyroid-stimulating hormone [TSH])

Hyperthyroidism

1. Biochemical monitoring as in hypothyroidism, plus serum thyroid-stimulating antibodies
2. Carbimazole
3. Partial thyroidectomy
4. Avoidance of radioiodide

Obesity

1. Monitoring of weight gain (optimal gain of between 4 to 9 kg)
2. Avoidance of heavy slimming

Neurological Diseases

Epilepsy

1. Preconceptional control of antiepileptic medication
2. Measurement of folic acid and antiepileptic drug concentrations
3. Adjustment of dosages of antiepileptic medications near term
4. Daily folic acid
5. Vitamin K injection for offspring

Migraine

1. Prostaglandin synthesis inhibitors, acetylsalicylic acid, and prochlorperazine
2. Adrenergic beta-receptor blocking agents
3. Avoidance of ergotamine derivatives

Note: Guideline developers considered but did not recommend $5HT_1$ antagonists (Triptans) during pregnancy and lactation because of insufficient experience of their use.

Disturbances of Cerebral Circulation

1. Treatment as for a non-pregnant patient
2. Avoidance of straining or pushing during delivery

Renal Diseases

1. Close observation of renal function and obstetric antenatal situation
2. Antibiotic treatment of asymptomatic bacteriuria with nitrofurantoin, cephalosporins, or mecillinam
3. Avoidance of pregnancy for 1 to 2 years after renal transplantation

Rheumatic Disorders

1. Acetylsalicylic acid, prostaglandin inhibitors, sulphasalazine, and glucocorticoids
2. In active systemic lupus erythematosus (SLE), prednisone, miniaspirin, or miniheparin

Note: Guideline developers considered but did not recommend the use of gold, hydroxyl-chloroquine, D-penicillamine, azathioprine, and cyclophosphamide.

Psychiatric Problems

1. Reconsideration of need for drug treatment, taking into account well-being of both mother and child
2. First generation antipsychotics (phenothiazines, thioxanthenes, haloperidol)
3. Tricyclic antidepressants (amitriptyline, imipramine)
4. Selective serotonin reuptake inhibitors (SSRIs) that have been in use for a long time (e.g., cipramil)
5. Discontinue psychopharmacological drugs as needed

Bronchial Asthma

1. Pharmacological therapy (inhaled $beta_2$-agonists, theophylline, inhaled glucocorticoids, cromolyn, some antihistamines, oral corticosteroids)
2. Treatment of status asthmaticus during labour as in non-pregnant patients

Cancer

1. Avoidance of all procedures (surgery, radiotherapy, administration of cytotoxic drugs) during first trimester
2. Treatment of each case individually with surgery, radiotherapy, and/or cytotoxic drugs, as appropriate
3. Avoidance of pregnancy for 2 years after surgery for breast cancer

MAJOR OUTCOMES CONSIDERED

- Maternal and neonatal safety
- Effectiveness of various treatments

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The evidence reviewed was collected from the Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effectiveness (DARE). In addition, the Cochrane Library and medical journals were searched specifically for original publications.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

A. **Quality of Evidence: High**

Further research is very unlikely to change confidence in the estimate of effect

- Several high-quality studies with consistent results
- In special cases: one large, high-quality multi-centre trial

B. **Quality of Evidence: Moderate**

Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

- One high-quality study
- Several studies with some limitations

C. **Quality of Evidence: Low**

Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

- One or more studies with severe limitations

D. **Quality of Evidence: Very Low**

Any estimate of effect is very uncertain.

- Expert opinion
- No direct research evidence
- One or more studies with very severe limitations

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence [A-D] supporting the recommendations are defined at the end of the "Major Recommendations" field.

General

- Poorly treated or untreated systemic disease impairs fertility; adequate management effectively restores fertility.
- Preconception examination and counselling by both the specialist treating the systemic disease and an obstetrician is essential for assessing individual risks of pregnancy and delivery.
- Systemic disease must be monitored closely throughout gestation in a high-risk pregnancy. Good collaboration between the prenatal clinic and maternity

hospital is essential (see the Finnish Medical Society Duodecim guideline "Antenatal Clinics and Specialist Care: Consultations, Referrals, Treatment Guidelines").

Heart and Vascular Diseases

- Cardiac output begins to rise during the first trimester of pregnancy and increases by 30 to 50%. This means an increased circulatory burden for the heart. Both heart rate and stroke volume increase, and peripheral vascular resistance falls.
- The ability of the cardiovascular system to react to physical strain is limited, especially during the third trimester.
- The axis of the heart shifts horizontally and slightly to the left because of the rise of the diaphragm, increasing the tendency of ectopic beats.
- During pregnancy the uterus causes obstruction of the vena cava in the supine position. This diminishes venous return. Therefore, a pregnant woman must be placed in a left lateral recumbent position for every examination or treatment that lasts for long.

Hypertension

- See the Finnish Medical Society Duodecim guidelines "Pregnancy and Blood Pressure" and "Antenatal Clinics and Specialist Care: Consultations, Referrals, Treatment Guidelines."
- Arterial blood pressure does normally not exceed 140/90 mmHg in pregnancy.
- Hypertension during pregnancy is associated with pre-eclampsia in 70% of patients, and chronic hypertension in 30% of patients.
- The incidence of chronic hypertension in Northern Europe is about 2 to 4%. The risk of hypertension increases after the age of 30 years.
- Foetal risks are connected with chronic placental insufficiency (e.g., small-for-gestational-age newborn and foetal hypoxia). The maternal risks in very severe hypertension are circulatory brain disturbances, heart failure, and complications resulting from superimposed pre-eclampsia.
- A slight or moderate rise of arterial blood pressure without albuminuria is not an indication of high risk. Close monitoring of the pregnancy in the outpatient clinic of the maternity hospital is important. If albuminuria occurs, the expectant mother must be admitted to the hospital.
- Most antihypertensive drugs are also useful during pregnancy. Of all the adrenergic beta-receptor blocking agents, labetalol is the most used and is the drug of choice. Atenolol can cause foetal growth retardation. Nifedipine is useful.
- Angiotensin-converting enzyme (ACE)-blocking agents are forbidden during pregnancy. They can increase the risk of foetal malformations. They also inhibit normal gestational development of the vascular system. Diuretic drugs are also not recommended because decreased plasma volume is associated with chronic hypertension and especially with pre-eclampsia.

Heart Diseases

- The increased load of pregnancy is most serious in connection with a pressure load, for example in mitral stenosis, but also in congenital heart diseases with

hypoxia. Mothers with mitral stenosis have an increased risk for atrial flimmer and acute failure in the form of pulmonary oedema.
- Maternal mortality risk in cases of Marfan's syndrome as well as in Eisenmenger's syndrome and in cardiomyopathy is about 50%.
- Obstetric patients with heart disease are not at risk if the functional capacity of the heart is classified into New York Heart Association (NYHA) Classes I or II (See the Finnish Medical Society Duodecim guideline "Chronic Heart Failure.").
- Maternal mortality in cases of NYHA Class III-IV heart disease is about 10%, especially if a full assessment of cardiac status and medical management was not performed prior to the pregnancy. The risk level is the same in pregnancy after myocardial infarction.
- Medical treatment is chosen according to the cardiac disease and the condition of the patient.

Thrombotic Complications

- The risk of recurrence of deep vein thrombosis or pulmonary embolism increases greatly during pregnancy.
- As basic laboratory tests, antithrombin III (AT_{III}), protein-C, and protein-S, as well as activated partial thromboplastin time (APTT), are needed to detect lupus anticoagulant syndrome.
- When earlier deep vein thrombosis or pulmonary embolism was associated with a lack of AT_{III}, protein-C, or protein-S, thrombosis prophylaxis has to be started on gestational week 6, and continued throughout pregnancy until 3 months since delivery. AT_{III} concentrate is also useful during labour.
- If an earlier thrombosis has occurred without a lack of AT_{III}, protein-C, or protein-S, the prophylactic treatment is started on gestational weeks 20 to 24 and ended 6 to 12 weeks after delivery.
- The drug of choice is low molecular weight heparin administered once daily (Ensom & Stephenson, 1999) [**C**]. Monitoring of the treatment is not needed. After the 24th week of gestation a double dose is needed as also when the mother weighs more than 75 kg.
- Subcutaneous unfractionated heparin as a dose of 7,500 to 12,500 IU can also be used; its use has declined. This treatment needs normal monitoring. Both low molecular weight heparin and subcutaneous heparin treatment have to be stopped for the time of labour, 12 hours before induction of labour.
- Warfarin is known as a teratogenic agent. Therefore, it is not useful in thrombosis prophylaxis during pregnancy except in patients with a cardiac prosthetic valve.
- See also the Finnish Medical Society Duodecim guideline " Inherited Thrombophilia."

Metabolic Disorders

Diabetes

- The number of mothers with impaired glucose tolerance is about 10-fold higher than that of women with type 1 diabetes.
- Pregnancy complicated by insulin-dependent diabetes is one of the most important risk groups in obstetrics today. Due to the low number of cases, diabetic control should be concentrated at university and central hospitals.

- Diabetes involves an increased risk of malformation but this may be reduced by good periconceptional glucose balance. Cooperation between obstetricians and internists throughout pregnancy is important.
- Careful monitoring at the prenatal clinic continues from the first trimester of pregnancy at 1 to 2 week intervals and a short stay in the antenatal ward of the obstetric department according to an individual plan is indicated for every patient.
- The maternal risks later in pregnancy are renal failure, disturbances in glucose balance, aggravation of diabetic retinopathy, increased risk of pre-eclampsia, and polyhydramnios. The foetal risks are malformations, spontaneous abortion and premature labour, intrauterine death, macrosomia with shoulder dystocia, and Erb's paresis. Neonatal adaptation problems are increased, including hypoglycaemia, hypocalcaemia, hyperbilirubinaemia, and respiratory distress syndrome.
- Insulin therapy is given as a multi-injection treatment. Peroral treatment with an antidiabetic drug is not possible because of foetal malformation risk.
- Very tight diabetic control may lead to maternal hypoglycaemia and is no more effective than tight control of diabetes during pregnancy.
- Vaginal delivery is planned near to term if obstetrically possible. Indications for Caesarean section are obstetric, such as pelvic disproportion, foetal distress in the first stage of labour, worsening pre-eclampsia, and abnormal foetal presentation. Maternal proliferative retinopathy and renal failure are also indications for Caesarean section.

Hypothyroidism

- Untreated hypothyroidism causes reduced fertility and increases risk of miscarriage.
- Thyroxine dosage needs to be increased by 25-50 micrograms during pregnancy. The dosage is increased by 25 micrograms as soon as the pregnancy begins; it is further adjusted according to the serum thyroid stimulating hormone (TSH) concentration so that this is maintained below 4 mU/L.
- Therapeutic balance is estimated before conception, during the first prenatal visit, and in gestational weeks 20 to 24 and 28 to 32. Slight hyperthyroidism is not dangerous for the foetus or the mother. After an operation for thyroid gland cancer, TSH concentrations must remain undetectable.
- Certain drugs, especially iron, disturb the absorption of thyroxine; these medications should be taken at different times.
- After delivery, thyroid substitution therapy can be reduced into the pregestational level.

Hyperthyroidism

- Undiagnosed and untreated hyperthyroidism may cause a spontaneous abortion or premature labour.
- Hyperthyroidism is difficult to identify in pregnancy because many of the symptoms and signs are similar to the changes in normal pregnancy (tachycardia, anxiety, peripheral vasodilatation, goitre, slight exophthalmus).
- Biochemical monitoring as in hypothyroidism, plus the level of serum thyroid-stimulating antibodies. Those antibodies can cross the placenta, and increase the risk of hypothyroidism of the newborn.

- A thyrostatic drug (carbimazole) is the most important treatment. Biochemical monitoring is essential to keep the serum free thyroxine level at a level slightly higher than normal. The risk of foetal goitre is only 1% in such cases.
- Partial thyroidectomy is sometimes needed. Treatment with radioiodide is not possible.

Obesity

- A maternal pregestational body weight of more than 90 kg is associated with a 4-fold risk of gestational hypertension and a 1.5-fold risk of gestational diabetes compared with normal-weight women.
- Obesity also increases the risk of thromboembolic complications, especially if bed rest during pregnancy or puerperium is needed.
- Foetal risk for macrosomia increases (Cedergren, 2004; Ehrenberg, Mercer, & Catalano, 2004; Sebire et al., 2001; Weiss et al., 2004) [**A**], which in turn is associated with prolonged labour, increased need for Caesarean section (Cedergren, 2004; Sebire et al., 2001; Weiss et al., 2004; Sheiner et al., 2004) [**A**], and shoulder dystocia.
- The acceptable weight gain for obese expectant mothers is not more than 4 to 9 kg. Heavy slimming during pregnancy is not recommended (Kramer & Kakuma, 2003) [**B**].

Neurological Diseases

Epilepsy

- Good preconceptional control of the antiepileptic medication is important.
- The general principle in antiepileptic medication is monotherapy, if possible. Drugs used before conception are usually continued during pregnancy.
- Children of epileptic mothers run a 1.5 to 2 times higher risk of major malformations than controls. Some teratogenicity is associated with antiepileptic drugs. For example, valproate is a cause of spina bifida in 1% of infants. Because of hypoxia, a generalised epileptic seizure is always more dangerous for the foetus than drug treatment. (Hiilesmaa, Bardy, & Teramo, 1985)
    - A healthy foetus will withstand the hypoxic episodes but they may be life-threatening for a sick foetus.
- Serum concentrations of folic acid and antiepileptic drugs must be measured monthly throughout pregnancy. Drug levels are often below the usual ranges because of increased plasma volume. Risk of convulsive seizure increases only slightly because the decrease in concentration of freely circulating drug is small. The dosage of antiepileptic drug should be increased near term due to increased risk of seizure during labour.
- Daily administration of folic acid is especially important during the first trimester.
- Vaginal delivery is possible. The indications for Caesarean section are obstetric, but the incidence of operative delivery is about twice that of controls. Vitamin K injection is essential for the offspring.
- Breastfeeding is usually possible. Large doses of phenemal and diazepam may cause somnolence in the newborn because of a high drug concentration in the breast milk.

Migraine

- Tension headache is more common than migraine during pregnancy.
- The incidence of migraine seizure is highest during the first and third trimester, seldom during the second trimester.
- Close to the delivery pre-eclampsia-like symptoms (vision disturbances, high blood pressure, headache, and subdiaphragmatic pain) cause differential diagnostic problems.
- Prostaglandin synthesis inhibitors and acetylsalicylic acid can be used during the first trimester of pregnancy, as well as prochlorperazine. Ergotamine derivatives are prohibited.
- Prostaglandin synthesis inhibitors are not used after week 32 of gestation because the foetal ductus arteriosus may close intrauterinely.
- 5-hydroxytryptamine ($5HT_1$) antagonists (triptans) are not used during pregnancy and lactation because of insufficient experience of their use.
- Adrenergic beta-receptor blocking agents, such as propranolol, may be suitable for prophylaxis in severe cases.

Disturbances of Cerebral Circulation

- Risk of thrombotic stroke is increased about tenfold during pregnancy. The number of spontaneous subarachnoid haemorrhages is also increased during gestation, as is the rupture of cerebral angiomas and aneurysms.
- Treatment of cerebral vascular disorders does not differ during pregnancy compared with non-pregnant patients. When the aneurysm is operated on, a subsequent pregnancy does not increase the risk of a cerebral attack. In non-operated patients pregnancy and delivery are relative contraindications because of increased risks. The indications for Caesarean section are obstetric. The delivery should be managed so that the mother has no need to strain or push.

Renal Diseases

- Renal blood flow and glomerular filtration increase by 30 to 50% during gestation. Renal tubular function also changes. Uric acid and creatinine clearance increase and the concentration of serum creatinine decreases. The normal level of serum creatinine is <80 micromoles/L. A degree of hydronephrosis and hydroureter also occurs, especially on the right side.
- When chronic renal failure with an increased level of serum creatinine, high blood pressure, and proteinuria develops, the pregnancy is complicated. Pregnancy is not recommended when the non-pregnant diastolic blood pressure exceeds 90 mmHg and the concentration of serum creatinine is 120 to 175 micromoles/L.
- In all cases, renal function, as well as the obstetric antenatal situation, must be observed closely in collaboration with a physician specializing in renal diseases.
- Hypertension and albuminuria occur in over 50% of even less severe cases of renal insufficiency, followed by poor placental function, growth retardation of the foetus, and premature labour.
- The prognosis of the pregnancy is greatly affected by lupus nephropathy, membranous glomerulonephritis, and scleroderma, even if the renal function tests are near normal. In such cases pregnancy is relatively contraindicated.

- Untreated asymptomatic bacteriuria is a cause of pyelonephritis in about 40% of cases. Therefore, antibiotic treatment with nitrofurantoin, cephalosporins, or mecillinam should be given during the first trimester of pregnancy.
- A patient with feverish pyelonephritis is best cared for in an obstetric antenatal ward. The antibiotic therapy is started parenterally, for example with cephalosporins, until the sensitivity of urinary bacteria to antibiotics has been determined. Peroral antibiotic therapy is continued for 3 weeks. The risk of recurrence is quite high during pregnancy and in puerperium. Therefore, in these cases long-term maintenance therapy for the remainder of the pregnancy and puerperium is needed: nitrofurantoin 50 milligrams (mg), cephalexin 250 mg, or mecillinam 200 mg in the evening.
- Pregnancy is not recommended earlier than 1 to 2 years after renal transplantation, if there are no problems with renal function or immunosuppressive therapy. Very close follow-up is needed, starting before conception.

Rheumatic Disorders

- The most problematic rheumatic disorders during pregnancy are rheumatoid arthritis and systemic lupus erythematosus (SLE).
- Pregnancy suppresses rheumatoid arthritis. 75% of women with rheumatoid arthritis have less pain and other symptoms already at the end of the first trimester in comparison with non-pregnant patients. Following delivery, the symptoms recur in 90% of cases and are usually more serious.
- Acetylsalicylic acid, prostaglandin inhibitors, sulphasalazine, and glucocorticoids are useful treatments. Gold, hydroxy-chloroquine, D-penicillamine, azathioprine, and cyclophosphamide are not recommended.
- SLE is always a serious threat to pregnancy. The probability of an exacerbation is more than 30%; no improvement of the disease is seen during pregnancy. The prognosis of the mother and the foetus is especially poor in cases with circulatory antibodies to phospholipids (e.g., cardiolipin or lupus anticoagulant antibodies) because of increased risk of thrombotic disorders (arterial thrombosis, fibrotic placenta, placental infarction, spontaneous abortion, foetal growth retardation, and intrauterine foetal death). When SLE is in an active phase, any treatment has only a minimal influence on the prognosis.
- The most often used treatment modalities include miniaspirin at a dose of 50 (–100) mg daily or low molecular weight (LMW) heparin or their combination. Oral prednisone 20 to 40 mg daily throughout pregnancy is used as well. SLE is so rare that no good controlled studies are available on the comparison between different treatment schedules.

Psychiatric Problems

- Some psychiatric drugs (e.g., phenothiazines) may reduce the likelihood of conception by increasing prolactin production. Sexual problems associated with emotional disorders may also be a reason for delayed conception.
- Pregnancy, delivery, and the postpartum period are always times of psychological stress for women. Earlier severe psychiatric disorders before pregnancy or during an earlier pregnancy, delivery, or puerperium present a major risk in subsequent gestation and puerperium. The risk is also increased when the husband has a history of psychopathology.

- The need for drug treatment should be reconsidered in pregnant women with the well-being of the mother and child taken into account. Drugs should not be interrupted suddenly. Lithium may increase the risk of congenital heart malformations. Phenothiazines and thioxanthenes are considered safe. There is some doubt concerning the use of tricyclic antidepressants, butyrophenones, and benzodiazepines in the first trimester of gestation.
- There is a suspected link between congenital cleft lip and palate and administration of benzodiazepine derivatives during the first 40 to 60 days of gestation. The risks are not obvious later in gestation.
- Tranquillizers taken in large doses close to the birth depress the newborn and cause somnolence and muscular atony.
- The use of the so-called first generation antipsychotics (phenothiazines, thioxanthenes, haloperidole) is safe during pregnancy.
- In the treatment of depression, respectively, the tricyclic antidepressants amitriptyline and imipramine are the safest.
    - When used close to the delivery, nortriptyline may cause more severe withdrawal symptoms in the newborn than other antidepressants.
    - Also the selective serotonin reuptake inhibitors (SSRIs) that have been in use for a long time (e.g., cipramil) are usable.
- Discontinuation of psychopharmacological drugs towards the end of pregnancy should take place only with strong indications and the situation should always be individually assessed.

Bronchial Asthma

- The prevalence of asthma in pregnancy is reported to be about 1%. The condition is worsened in every third woman during pregnancy, but improves in the same proportion of cases. Bronchial asthma is a minor problem in the normal course of gestation.
- The use of inhaled beta$_2$-agonists, theophylline, inhaled glucocorticoids, as well as cromolyn and some antihistamines is not known to be associated with congenital malformation. Oral corticosteroids are sometimes also needed for short periods.
- Status asthmaticus during labour is a problem, as poor maternal oxygenation can result in foetal hypoxia. The treatment is similar to that in non-pregnant patients. The risk of Caesarean section is increased because of hypoxia.

Cancer in Pregnancy

- The prevalence of carcinoma during pregnancy is about 1:1000-2000 deliveries (i.e., similar or lower than in non-pregnant women of comparable age).
- The most common type of cancer during pregnancy is breast cancer, followed by leukaemias, and uterine cervical, ovarian, and intestinal cancer.
- Transplacental transmission of carcinoma cells is possible only in malignant melanoma.
- All procedures (surgery, radiotherapy, and administration of cytotoxic drugs) are dangerous for the foetus during the first trimester. Cytotoxic drugs are especially teratogenic during organogenesis of the foetus, as is radiotherapy treatment if given below the diaphragm. Risk of spontaneous abortion is also increased during that time.

- It is important to treat every case individually, in collaboration with the patient.
- The outcome is mainly seen in 2 years: if the prognosis is good, no signs of recurrence of the cancer are seen; if it is poor, symptoms and signs of cancer recur.
- After surgery for breast cancer, pregnancy should be avoided for 2 years. (Previous recommendation: 5 years.) There is no evidence that pregnancy itself affects the prognosis; however, examination of the breasts is more difficult in pregnant than in non-pregnant women.

Related Resources

Cochrane Reviews

- Treatment of impaired glucose tolerance in pregnancy seems to result in beneficial perinatal outcomes, but there is sparse data for conclusions (Tuffnell, West, & Walkinshaw, 2003) [**D**].
- Continuous subcutaneous insulin infusion is probably not superior to multiple daily injections for pregnant women with diabetes (Farrar, Tuffnell, & West, 2007) [**C**]

Other Evidence Summaries

- Selective serotonin reuptake inhibitors given in late pregnancy seem to have subtle adverse effects on the newborn, but there is insufficient evidence from high-quality trials (Lattimore et al., 2005) [**D**].
- Some selective serotonin-reuptake inhibitors may increase the risks for some specific defects, but the specific defects implicated are rare and the absolute risks are small (Louik et al., 2007) [**C**]

Definitions:

Levels of Evidence

A. **Quality of Evidence: High**

Further research is very unlikely to change confidence in the estimate of effect

- Several high-quality studies with consistent results
- In special cases: one large, high-quality multi-centre trial

B. **Quality of Evidence: Moderate**

Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

- One high-quality study
- Several studies with some limitations

C. **Quality of Evidence: Low**

Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

- One or more studies with severe limitations

D. **Quality of Evidence: Very Low**

Any estimate of effect is very uncertain.

- Expert opinion
- No direct research evidence
- One or more studies with very severe limitations

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Concise summaries of scientific evidence attached to the individual guidelines are the unique feature of the Evidence-Based Medicine Guidelines. The evidence summaries allow the clinician to judge how well-founded the treatment recommendations are. The type of supporting evidence is identified and graded for select recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of systemic diseases in pregnancy to maintain maternal and fetal well-being and reduce risk of adverse effects associated with treatment or lack of treatment of systemic disease

POTENTIAL HARMS

- Atenolol can cause foetal growth retardation.
- Warfarin is known as a teratogenic agent.
- Certain drugs, especially iron, disturb the absorption of thyroxine; these medications should be taken at different times.
- The risk of foetal goitre is only 1% with carbimazole.
- Some teratogenicity is associated with antiepileptic drugs. For example, valproate is a cause of spina bifida in 1% of infants.
- Large doses of phenemal and diazepam may cause somnolence in the newborn because of a high drug concentration in the breast milk.

- Prostaglandin synthesis inhibitors are not used after week 32 of gestation because the foetal ductus arteriosus may close intrauterinely.
- Lithium may increase the risk of congenital heart malformations.
- There is a suspected link between congenital cleft lip and palate and administration of benzodiazepine derivatives during the first 40 to 60 days of gestation.
- Tranquillizers taken close to the birth depress the newborn and cause somnolence and muscular atony.
- When used close to delivery, nortriptyline may cause more severe withdrawal symptoms in the newborn than other antidepressants.
- All procedures for cancer (surgery, radiotherapy, and administration of cytotoxic drugs) are dangerous for the foetus during the first trimester. Cytotoxic drugs are especially teratogenic during organogenesis of the foetus, as is radiotherapy treatment if given below the diaphragm. Risk of spontaneous abortion is also increased during that time.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Angiotensin-converting enzyme (ACE)-blocking agents are forbidden during pregnancy. They can increase the risk of foetal malformations. They also inhibit normal gestational development of the vascular system. Diuretic drugs are also not recommended because decreased plasma volume is associated with chronic hypertension and especially with pre-eclampsia.
- Peroral treatment with an antidiabetic drug is not possible because of foetal malformation risk.
- Treatment of hyperthyroidism in pregnancy with radioiodide is not possible.
- Ergotamine derivatives are prohibited as treatment for migraine during pregnancy.
- Prostaglandin synthesis inhibitors are not used to treat migraine after week 32 of gestation because the foetal ductus arteriosus may close intrauterinely.
- In patients with non-operated aneurysms, pregnancy and delivery are relative contraindications because of increased risks.
- Pregnancy is relatively contraindicated in patients with lupus nephropathy, membranous glomerulonephritis, and scleroderma.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Finnish Medical Society Duodecim. Systemic diseases in pregnancy. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007 Apr 13 [Various].

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

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GUIDELINE DEVELOPER(S)

Finnish Medical Society Duodecim - Professional Association

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Finnish Medical Society Duodecim

GUIDELINE COMMITTEE

Editorial Team of EBM Guidelines

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Author: Seppo Saarikoski

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Finnish Medical Society Duodecim. Systemic diseases in pregnancy. In: EBM Guidelines. Evidence-Based Medicine

[Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2006 Aug 30 [Various].

GUIDELINE AVAILABILITY

This guideline is included in a CD-ROM titled "EBM Guidelines. Evidence-Based Medicine" available from Duodecim Medical Publications, Ltd, PO Box 713, 00101 Helsinki, Finland; e-mail: info@ebm-guidelines.com; Web site: www.ebm-guidelines.com.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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